Systematic review on urine albumin testing for early detection of diabetic complications

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Executive summary

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Executive summary

Background

Microalbuminuria is predictive of adverse events in patients with type 1 and type 2 diabetes mellitus (DM) and might be a useful screening tool to help to target treatment more effectively. There is evidence of decreasing prevalence of diabetic complications, particularly nephropathy and retinopathy, probably due to improved treatment of all patients with diabetes irrespective of urine albumin status. Hence, there is uncertainty about the value of a national screening programme for microalbuminuria, which would be justified only if patients identified with microalbuminuria are at greater risk, cannot be otherwise currently identified and derive greater treatment benefit than patients with normoalbuminuria. This systematic review has sought evidence to support screening for microalbuminuria by evaluating end-points in patients with DM who are microalbuminuric compared with those patients who are normoalbuminuric.

Research questions

Question 1: In patients with type 1 or type 2 DM, what is the evidence that microalbuminuria is an independent prognostic factor for the development of diabetic complications? The following complications were assessed: mortality (Review 1), the development and progression of retinopathy (Review 2) and the development of renal failure (Review 3).

Question 2: In subjects with type 1 or type 2 DM and microalbuminuria, what is the evidence that improved glycaemic control (Review 4) or improved blood pressure control, including the use of angiotensin-converting enzyme (ACE) inhibitors in normotensive patients (Review 5) has influenced the development of diabetic complications more than in those without microalbuminuria?

Methods

The steering group prepared a protocol for peer review by an external expert panel: it included selection criteria for data extraction and required two independent reviewers to undertake article selection and review. The literature was explored electronically up until January 2002. Completeness was assessed using hand-searching of major journals. Lead authors were contacted when data extraction was not possible or when a study was unpublished. Random effects meta-analysis was used to obtain combined estimates of relative risk (RR). Funnel plots, trim and fill methods and meta-regression were used to assess publication bias and sources of heterogeneity.

Results

In patients with type 1 or type 2 DM, is there a prognostic relationship between the presence of microalbuminuria and mortality?

In patients with type 1 DM and microalbuminuria there is an RR of all-cause mortality of 1.8 [95% confidence interval (CI) 1.5 to 2.1] that is unaffected by adjustment for confounders. Similar RRs were found for other mortality end-points: cardiovascular disease (CVD) mortality 1.9 (95% CI 1.3 to 2.9), coronary heart disease (CHD) mortality 2.1 (95% CI 1.2 to 3.5) and aggregate CVD morbidity and mortality 2.0 (95% CI 1.5 to 2.6). After adjusting for confounders, the data sets supporting the relationship of microalbuminuria with these last three end-points were small and/or lacked consensus, and further studies are required with adjustments for covariates to confirm a relationship.

Similar results were observed for type 2 DM: an RR of 1.9 (95% CI 1.7 to 2.1) for all-cause mortality, 2.0 (95% CI 1.7 to 2.3) for CVD mortality and 2.3 (95% CI 1.7 to 3.1) for CHD mortality. Adjustment for confounders only very slightly reduced these values. For all-cause mortality, age of cohort was inversely related to the RR. It was not possible to calculate a combined RR for aggregate CVD morbidity and mortality, although it was evident that no consensus exists.

In patients with type 1 or type 2 DM, is there a prognostic relationship between the presence of microalbuminuria and the development and progression of retinopathy?

In patients with type 1 DM, there is evidence that microalbuminuria or raised albumin ▶

excretion rate has only weak, if any, independent prognostic significance for the incidence of retinopathy and no evidence that it predicts progression of retinopathy. There is strong evidence for the independent prognostic significance of microalbuminuria or raised albumin excretion rate for the development of proliferative retinopathy (crude RR of 4.1, 95% CI 1.8 to 9.4).

In patients with type 2 DM, there is no evidence that microalbuminuria or raised albumin excretion rate has any independent prognostic significance for the incidence of retinopathy. The limited evidence indicates little if any prognostic relationship between microalbuminuria and the progression of retinopathy or development of proliferative retinopathy.

In patients with type 1 or type 2 DM, is there a prognostic relationship between the presence of microalbuminuria and the development of renal failure?

In patients with type 1 DM and microalbuminuria there is an RR of developing end-stage renal disease (ESRD) of 4.8 (95% CI 3.0 to 7.5) and a higher relative risk (7.5, 95% CI 5.4 to 10.5) of developing clinical proteinuria. The two studies that reported change in glomerular filtration rate (GFR) both reported a significantly greater fall in GFR in patients with microalbuminuria.

In patients with type 2 DM, similar RRs were observed: 3.6 (95% CI 1.6 to 8.4) for developing ESRD and 7.5 (95% CI 5.2 to 10.9) for developing clinical proteinuria. In addition, a significantly greater decline in GFR was seen in the microalbuminuria group of 1.7 (95% CI 0.1 to 3.2) ml per minute per year compared with those who were normoalbuminuric.

In adults with type 1 or type 2 DM and microalbuminuria at baseline, the numbers progressing to clinical proteinuria (19% and 24%, respectively) and those regressing to normoalbuminuria (26% and 18%, respectively) did not differ significantly. In children with type 1 DM, regression (44%) was significantly more frequent than progression (15%).

In patients with type 1 or type 2 DM and microalbuminuria, does improved glycaemic control reduce the rate of development of secondary diabetic complications?

In patients with type 1 DM and microalbuminuria, there is no evidence as to whether improved glycaemic control has any effect on the incidence of CVD, the incidence or progression of retinopathy, the development of proliferative retinopathy, the development of ESRD or the decline in GFR; there is inconclusive evidence as to whether there is any effect on the development of clinical proteinuria (RR 0.6, 95% CI 0.3 to 1.2). Among patients not stratified by albuminuria, improved glycaemic control might be beneficial with respect to CVD and is beneficial in reducing both the incidence and progression of retinopathy and the development of proliferative retinopathy. There are no data with respect to developing ESRD and limited evidence showing little effect on GFR decline. The Diabetes Control and Complications Trial (DCCT) provides convincing evidence of a beneficial effect in reducing the development of clinical proteinuria in a predominantly normoalbuminuric cohort and also of preventing the development of microalbuminuria.

In patients with type 2 DM and microalbuminuria, there is no evidence as to whether improved glycaemic control has any effect on the incidence of CVD, the incidence or progression of retinopathy or the development of ESRD. There is evidence from one trial that improved glycaemic control in this group has little if any effect on the decline in GFR and data on the progression to clinical proteinuria are inconclusive. Among patients not stratified by albuminuria, there is little evidence of improved glycaemic control reducing CVD, but good evidence of a beneficial effect on the incidence and progression of retinopathy. There is inconclusive evidence of any effect on the development of ESRD, but one trial showed a lesser decline in GFR with improved glycaemic control and there was some evidence for slowing the development of clinical proteinuria. There was also strong evidence that improved glycaemic control prevented or slowed progression from normoalbuminuria to microalbuminuria, although this was not the focus of this analysis.

In patients with type 1 or type 2 DM and microalbuminuria, does treatment with antihypertensive drugs reduce the rate of development of secondary diabetic complications?

Trials in patients with type 1 DM and microalbuminuria have mostly included normotensive subjects and focused on the effect of antihypertensive agents, particularly ACE inhibitors, for their possible renoprotective benefits. There were no trials with CVD as an end-point. There is evidence from one large ►

trial that normotensive patients with type 1 DM treated with an ACE inhibitor show a reduced risk of progression of retinopathy, but there was no evidence of added benefit for patients with microalbuminuria. There were no trials with ESRD as an end-point. In the eight trials evaluating the effects of ACE inhibitors on GFR in normotensive microalbuminuric patients, there was no evidence of a consistent treatment effect. There is strong evidence from 11 trials in normotensive patients with microalbuminuria of a beneficial effect of ACE inhibitor treatment on the risk of developing clinical proteinuria (RR = 0.36, 95% CI 0.22 to 0.58) and on the risk of regression to normoalbuminuria (RR = 5.3, 95% CI 2.5 to 11.5). There were no trials in hypertensive subjects with microalbuminuria comparing different antihypertensive regimes.

In patients with type 2 DM and microalbuminuria, whether hypertensive or not, there is evidence from one trial that patients with microalbuminuria obtain additional cardiovascular benefit from an ACE inhibitor. Evidence from one trial also showed a beneficial effect on the development of retinopathy in normotensive type 2 patients, but no difference in the treatment effect between normoalbuminuric and microalbuminuric patients. In hypertensive subjects, neither of the two trials examining progression of retinopathy in relation to intensive blood pressure control, or the two trials comparing the effects of different antihypertensive agents, examined this in the microalbuminuric subgroup. There were no relevant trials with ESRD as an end-point in hypertensive or normotensive microalbuminuric patients. There is limited evidence that treatment of hypertensive microalbuminuric type 2 diabetic patients with blockers of the renin–angiotensin system is associated with preserved GFR, but also evidence of no differences in GFR in comparisons with other antihypertensive agents. The data on GFR in normotensive cohorts are inconclusive. In normotensive type 2 patients with microalbuminuria there is evidence from three trials (all enalapril) of a reduction in risk of developing clinical proteinuria (RR 0.28, 95% CI 0.15 to 0.53); in hypertensive patients there is evidence from one placebo-controlled trial (irbesartan) of a reduction in this risk. Intensive compared with moderate blood pressure control did not affect the rate of progression of microalbuminuria to clinical proteinuria in the one available study. There is inconclusive evidence from four trials of any difference in the proportions of hypertensive patients progressing from microalbuminuria to clinical proteinuria when ACE inhibitors are compared with other antihypertensive agents (RR 0.74, 95% CI 0.44 to 1.24), and in one trial regression was two-fold higher with lisinopril (26%) than with nifedipine (14%).

Implications for healthcare

Patients with diabetes at highest risk of developing major complications can predominantly be identified through determination of risk factors such as glycosylated haemoglobin (HbA_{1c}), blood pressure and lipid profile. Glycaemic control is the first aim of diabetic therapy. The most pronounced benefits of glycaemic control identified in this review are on retinal and renal complications in both normoalbuminuric and microalbuminuric patients considered together, with little or no evidence of any greater benefit in those with microalbuminuria. Hence, microalbuminuric status may be a false boundary when considering the benefits of glycaemic control. Classification of a person as normoalbuminuric must not serve to suggest that they will derive less benefit from optimal glycaemic control than a person who is microalbuminuric.

When considering the value of urine albumin in identifying patients with diabetes who require the introduction of antihypertensive medication (which is currently the only optional medical therapy to reduce albumin excretion), the following conclusions can be drawn:

- With regard to hypertension, there was very little evidence from this systematic review that identifying those patients who also had microalbuminuria was of any additional benefit, since all patients with diabetes and hypertension benefit from improved blood pressure control.
- This review provides evidence that microalbuminuria surveillance of patients with type 1 or type 2 diabetes who are normotensive (and not on antihypertensive therapy) may be effective, since antihypertensive therapy with an ACE-inhibitor substantially reduces their risk of progressing to clinical proteinuria and confers cardiovascular benefits, and these patients cannot be otherwise identified. It is likely that patients who are normotensive on antihypertensive treatment but who remain microalbuminuric would derive similar benefit, although they are highly likely to be on ACE inhibitor treatment already. All patients with microalbuminuria are also at increased mortality risk, even after adjustment for ▶

confounding factors, and patients with type 2 DM are also at increased risk of CVD and CHD mortality. Hence, assessment of cardiovascular risk and implementation of ACE inhibitor therapy should be considered in normotensive patients with microalbuminuria. Preliminary economic evaluation was inconclusive and further work in this area is required.
- In the authors' opinion, there is insufficient evidence to state that universal screening for microalbuminuria is of benefit to all patients with either type 1 or type 2 diabetes at present and indeed, if negative, it may provide false reassurance in the presence of suboptimal glycaemic and blood pressure control.
- Urine albumin measurement may be a useful indicator of the response to antihypertensive therapy, but does not have a proven role within the microalbuminuric range in modulating therapy over and above the measurement of blood pressure while the patient remains hypertensive, and this is not an indication for its use as a screening test.

Recommendations for research

The recommendations that follow are those that, in the authors' opinion, are the most important.

- What is the annual rate of development of microalbuminuria in patients with type 1 and type 2 DM who initially screen normoalbuminuric, and which risk factors predict the development of microalbuminuria? A systematic review of the literature is suggested.
- What are the factors that determine regression of microalbuminuria in adults and children with DM? Is this accompanied by reduction of risk of complications and why is regression rate apparently higher in children?
- There is a need for further economic evaluation of screening for microalbuminuria in type 1 and type 2 DM considering different strategies such as those used in a preliminary study considering blood pressure control (Appendix 2) and also incorporating glycaemic control.
- How variable is the analytical classification of patients as microalbuminuric and which analytical performance criteria (especially with regard to bias at low concentration) are required to standardise urine screening tests for detecting microalbuminuria?
- What is the effect of lipid-lowering therapy on urine albumin excretion in patients with microalbuminuria and normoalbuminuria?
- Does patient knowledge of their urine albumin status increase their compliance with medication and lifestyle advice over and above any effect on compliance derived from knowledge of their HbA_{1c} and blood pressure? Is any gain at the expense of increased emotional stress?
- Can antihypertensive therapy in hypertensive patients with microalbuminuria be better tailored to the individual patient and improve outcomes by using urine albumin measurements in conjunction with blood pressure to adjust treatment compared with blood pressure targets alone?

Publication

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NHS R&D HTA Programme

The research findings from the NHS R&D Health Technology Assessment (HTA) Programme directly influence key decision-making bodies such as the National Institute for Health and Clinical Excellence (NICE) and the National Screening Committee (NSC) who rely on HTA outputs to help raise standards of care. HTA findings also help to improve the quality of the service in the NHS indirectly in that they form a key component of the 'National Knowledge Service' that is being developed to improve the evidence of clinical practice throughout the NHS.

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The research reported in this monograph was commissioned by the HTA Programme as project number 96/33/02. The contractual start date was in June 1998. The draft report began editorial review in May 2002 and was accepted for publication in March 2005. As the funder, by devising a commissioning brief, the HTA Programme specified the research question and study design. The authors have been wholly responsible for all data collection, analysis and interpretation, and for writing up their work. The HTA editors and publisher have tried to ensure the accuracy of the authors' report and would like to thank the referees for their constructive comments on the draft document. However, they do not accept liability for damages or losses arising from material published in this report.

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